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The fibrogenic niche in kidney fibrosis: components and mechanisms

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Abstract | Kidney fibrosis, characterized by excessive deposition of extracellular matrix (ECM) that leads to tissue scarring, is the final common outcome of a wide variety of chronic kidney diseases. Rather than being distributed uniformly across the kidney parenchyma, renal fibrotic lesions initiate at certain focal sites in which the fibrogenic niche is formed in a spatially confined fashion. This niche provides a unique tissue microenvironment that is orchestrated by a specialized ECM network consisting of de novo-induced matricellular proteins. Other structural elements of the fibrogenic niche include kidney resident and infiltrated inflammatory cells, extracellular vesicles, soluble factors and metabolites. ECM proteins in the fibrogenic niche recruit soluble factors including WNTs and transforming growth factor-β from the extracellular milieu, creating a distinctive profibrotic microenvironment. Studies using decellularized ECM scaffolds from fibrotic kidneys show that the fibrogenic niche autonomously promotes fibroblast proliferation, tubular injury, macrophage activation and endothelial cell depletion, pathological features that recapitulate key events in the pathogenesis of chronic kidney disease. The concept of the fibrogenic niche represents a paradigm shift in understanding of the mechanism of kidney fibrosis that could lead to the development of non-invasive biomarkers and novel therapies not only for chronic kidney disease, but also for fibrotic diseases of other organs.

Chronic kidney disease (CKD) affects 8–15% of the global population and is characterized by loss of kidney function[1,2]. Approximately 800 million people have CKD worldwide and the incidence and prevalence are increasing[3]. CKD can progress to kidney failure, a devastating condition that requires life-saving kidney replacement therapy. Kidney fibrosis is considered to be the final common pathway in the evolution of virtually all types of CKD, irrespective of the initial cause of disease. In the past few decades, the nephrology community has made great efforts to decipher the mechanisms of kidney fibrosis and to develop therapeutic strategies. However, knowledge of the pathobiology of kidney fibrosis remains limited and the identification of strategies to prevent and/or treat fibrotic CKD is a daunting challenge[4,5]. Current therapeutic options for CKD are scarce and often ineffective, and no treatment is specifically targeted at kidney fibrosis[4,5]. This lack of success necessitates rethinking the fundamental mechanisms that drive kidney fibrosis and identifying new targets for therapeutic intervention.

Kidney injury can lead to the formation of a unique tissue microenvironment that undergoes dynamic changes in composition and contents during the evolution of injury repair and tissue remodelling. In particular, following a variety of insults, the extracellular matrix (ECM) proteins undergo qualitative and quantitative changes, which affect the activation and function of surrounding cells and change their phenotypes and trajectories. We proposed the term fibrogenic niche to describe the special tissue microenvironment that promotes fibroblast activation in organ fibrosis[6]. Detailed characterization of this niche is necessary and imperative to delineate the effect of the ECM microenvironment on fibroblast activation, inflammation and vascular homeostasis. Such characterization could be an innovative approach to identifying the mechanisms of kidney fibrosis. In this article, we review the composition, function and mechanisms of action of the fibrogenic niche in kidney fibrosis. We also discuss the potential implications of the fibrogenic niche hypothesis for the future diagnosis and treatment of fibrotic diseases.

Major events of kidney fibrogenesis

Studies using experimental models and kidney biopsy samples from patients with CKD have demonstrated that the distribution of fibrosis across the kidney parenchyma is neither uniform nor random[7]. Instead, fibrosis usually initiates from focal sites in which interstitial fibroblasts are activated, proliferate and produce large amounts of ECM components. These fibrotic foci often have clean boundaries that separate them from the surrounding area

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Key points

- Kidney fibrosis initiates at certain focal sites in which the fibrogenic niche is formed; this niche provides a specialized microenvironment that triggers fibroblast activation and induces fibrotic lesions.
- The structural elements of the fibrogenic niche include kidney resident and infiltrated inflammatory cells, extracellular matrix (ECM) network, extracellular vesicles, soluble factors and metabolites.
- The fibrogenic niche is orchestrated by a specialized ECM network that consists of structurally unrelated, de novo-induced matricellular proteins such as tenascin C, connective tissue growth factor, fibrillin 1 and periostin.
- Decellularized ECM scaffolds from fibrotic kidneys spontaneously promote fibroblast proliferation, tubular epithelial-to-mesenchymal transition, macrophage activation and endothelial cell apoptosis, and therefore recapitulate major events in the pathogenesis of chronic kidney disease.
- Components of the fibrogenic niche such as tenascin C recruit various soluble factors from the extracellular milieu, including WNTs, hedgehog and transforming growth factor-β, resulting in a distinctive microenvironment with high levels of profibrotic factors.
- The development of therapies that target and disrupt the formation of the fibrogenic niche could be a novel and effective strategy for the treatment of fibrotic chronic kidney disease.

with normal tissue architecture (FIG. 1a). Although the reasons why fibroblasts in distinctive sites of the kidney parenchyma respond differently after the same injury are largely unknown, it has long been thought that a specialized niche or tissue microenvironment — that we have termed the fibrogenic niche[6] — determines the focal activation of fibroblasts in discrete locations. The concept of the fibrogenic niche has also been applied to liver and lung fibrosis[8–11], highlighting the similarities between processes of tissue fibrogenesis in different organs.

Kidney fibrogenesis is a stepwise process; formation of the fibrogenic niche is followed by progressive ECM deposition and expansion, which leads to the formation of fibrotic foci scattered throughout the kidney parenchyma and eventually widespread tissue fibrosis[6]. A highly dynamic and complex series of cellular events take place in the fibrogenic environment, including kidney cell injury, inflammatory cell infiltration, myofibroblast activation, tubular atrophy and microvascular rarefaction[6,12–18] (FIG. 1b). Fibroblasts and perivascular pericytes are primed to proliferate, acquire a myofibroblast phenotype by expressing α-smooth muscle actin (αSMA) and become the principal matrix-producing cells. Fibroblast activation is accompanied, and perhaps preceded, by the infiltration of inflammatory cells such as neutrophils, lymphocytes and macrophages. Tubular epithelial cells undergo a diverse array of changes, including partial epithelial-to-mesenchymal transition (partial EMT), cell-cycle arrest, cellular senescence and apoptosis, leading to tubular atrophy. Capillary endothelial cells are also prone to injury and undergo senescence and apoptosis, resulting in microvascular rarefaction. All of these cellular components could potentially contribute to the formation of the fibrogenic niche by secreting ECM components, extracellular vesicles, soluble factors and metabolites.

Structural elements of the fibrogenic niche

Similar to the stem cell niche[19,20], the fibrogenic niche is composed of a wide variety of structural elements, including kidney resident cells, such as tubular cells, peritubular capillary endothelial cells, pericytes, interstitial fibroblasts and dendritic cells; infiltrated inflammatory cells such as neutrophils, T cells and macrophages; extracellular vesicles, secreted soluble factors and a specialized ECM network (FIG. 2). Tubular cells are the major targets of various insults and are particularly susceptible to damage. They respond to insults in various ways, including partial EMT, cell-cycle arrest and senescence[21–25]. Despite these different responses, the common and convergent consequence of tubular responses is that the cells produce and secrete a large amount of extracellular vesicles and profibrotic factors[13,26]. In particular, senescent cells acquire a senescence-associated secretory phenotype and secrete high levels of pro-inflammatory and profibrotic cytokines, chemokines, proteases and growth factors[27–29]. Therefore, an extraordinarily high level of extracellular vesicles and secreted soluble factors is likely present within the fibrogenic niche.

The fact that the fibrogenic niche is enriched with extracellular vesicles and profibrotic factors makes it an exceptional setting for fibroblast expansion. As extracellular vesicles are secreted by cells into the extracellular space, their concentration gradients depend on the distance from their cellular sources. In addition, extracellular vesicle membranes often express integrin receptors[30], which could orientate and facilitate their homing in the fibrogenic niche. The three main subtypes of extracellular vesicles, exosomes, microvesicles and apoptotic bodies, have distinct mechanisms of biogenesis, release pathways, sizes and contents[31–33]. Extracellular vesicles carry a cargo of proteins, mRNA, microRNA, long non-coding RNA, lipids and metabolites, and mediate intercellular signal exchanges in a robust and wholesale fashion.

Secreted soluble factors in the fibrogenic niche include transforming growth factor-β (TGFβ), fibroblast growth factor 2 (FGF2), platelet-derived growth factor (PDGF), IL-6, WNTs and sonic hedgehog (SHH). Most, if not all, of these secreted factors are potent inducers of fibroblast activation[34,35]. When injury persists, vascular rarefaction owing to endothelial cell dropout leads to local hypoxia, hypoperfusion and altered metabolites, further propagating the fibrogenic signals[36]. The fibrogenic niche not only provides the ideal environment for fibroblast activation and proliferation but also negatively affects the regenerative capacity and plasticity of surviving parenchymal cells, thereby hampering injury repair and kidney regeneration[37].

Another major structural element of the fibrogenic niche is the specialized ECM network, a 3D scaffold consisting of ECM proteins such as collagens, fibronectin, laminins, matricellular proteins and proteoglycans, which provide structural and biochemical support to surrounding cells[11,38]. After kidney injury, structural ECM proteins such as type I collagen and fibronectin are deposited and accumulate, leading to a dramatic increase in ECM protein quantity. The composition of the ECM proteins evolves in a temporally and spatially specific fashion, with de novo induction of multiple matricellular proteins. These changes lead to the assembly of a specialized profibrotic ECM network that

Partial epithelial-to-mesenchymal transition (Partial EMT). Tubular epithelial cells undergo a process of partial EMT in vivo in which they exhibit some phenotypic changes but stay within the tubular compartment. Partial EMT could be viewed as a transitional stage in which epithelial cells can further regress to cell-cycle arrest and senescence or return to normal epithelia.

Extracellular vesicles
Lipid bilayer-encircled particles that are released from almost all cell types and carry a cargo of proteins, mRNAs, microRNAs, long non-coding RNAs, lipids and metabolites. Extracellular vesicles can mediate cell–cell communication and signal exchange and are thought to have important roles in regulating biological processes including embryogenesis, injury repair and regeneration and the pathogenesis of disease.

Stem cell niche
A specific tissue microenvironment in which stem cells are present in an undifferentiated and self-renewable state.

Kidney tissue scaffolds (KTS). Decellularized extracellular matrix scaffold derived from normal or diseased kidneys that retains the critical structural, mechanical and physiological properties of renal structures.

controls cell adhesion, cell–cell communication and cellular behaviours focally in the 3D context.

The fibrogenic niche is a spatially confined microenvironment within the injured kidney. How the fibrogenic niche is initially organized in a particular area and spatially restricted to that location is unknown. The cellular components of the fibrogenic niche, particularly the infiltrated inflammatory cells, are motile, whereas extracellular vesicles, soluble factors and metabolites diffuse according to their concentration gradients. These properties render them unsuitable to settle and orchestrate the formation of the fibrogenic niche. By contrast, the ECM network is stationary. Once deposited in a certain location, ECM components usually settle in the area with a clean borderline, a scenario in harmony with niche formation. We therefore propose that the ECM functions as the anchor of the fibrogenic niche and dictates where the niche assembles by recruiting cellular components, extracellular vesicles and secreted factors from the surrounding extracellular milieu.

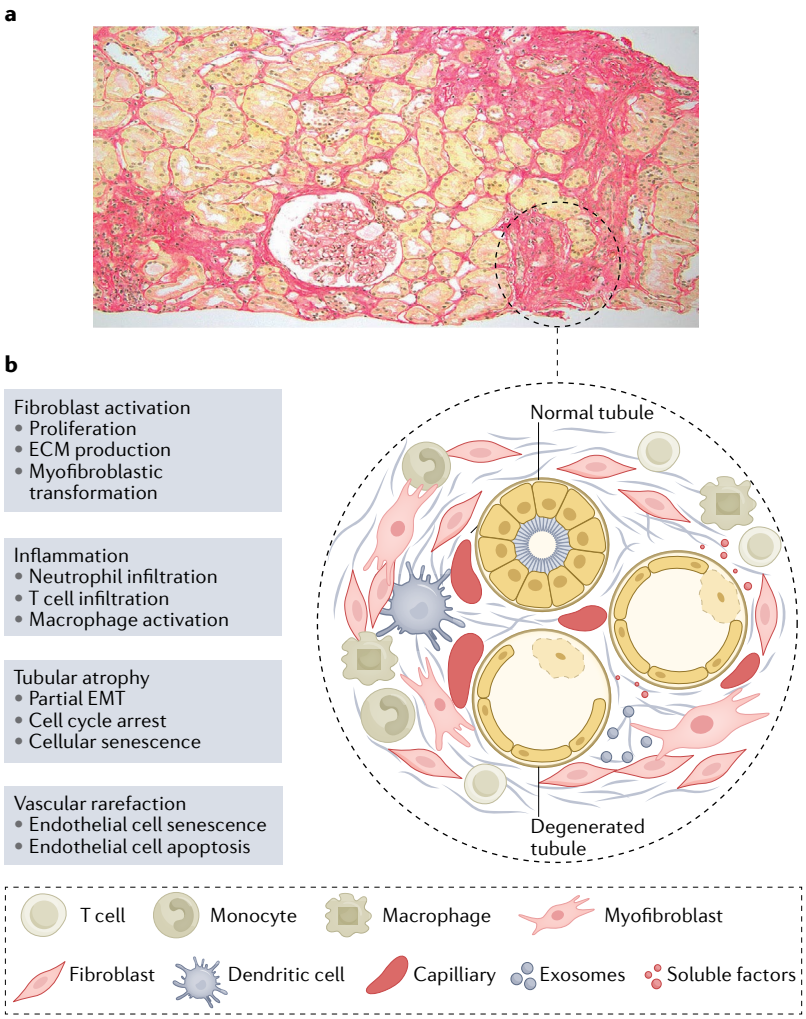

Fig. 1 | **Renal fibrosis initiates at distinctive focal sites of the kidney parenchyma.** **a** | Sirius red (collagen) staining showing a fibrotic focus (dashed circle) in a human kidney biopsy sample from a patient with chronic kidney disease. Strong staining for collagens is not homogeneous across the kidney parenchyma, and the fibrotic focus can be distinguished from the normal tissue with a clean boundary. **b** | The major cellular events that occur in the fibrotic foci after kidney injury include fibroblast activation, tubular atrophy, infiltration of inflammatory cells and vascular rarefaction. ECM, extracellular matrix; EMT, epithelial-to-mesenchymal transition. Part **a** reproduced with permission from REF.[7].

ECM components of the fibrogenic niche

Given the crucial role of the ECM network in establishing the fibrogenic niche, it is imperative to identify its molecular composition and investigate the dynamic changes in its constituents during kidney fibrosis. The first step in achieving this goal is to develop innovative technologies to systematically analyse ECM proteins without the interference of other elements of the fibrogenic niche. We adapted a technique to prepare decellularized kidney tissue scaffolds (KTS) from normal and fibrotic kidneys. The cellular contents, extracellular vesicles and soluble factors are eliminated from these KTS but the 3D structure and composition of the ECM is preserved[6]. Decellularized tissue scaffolds retain biological activity and have been widely used in the field of biomedical engineering and regenerative medicine[39–41]. Using an unbiased, mass spectrometry proteomics approach, we analysed the ECM components of normal and CKD kidneys[42,43]. We identified approximately 1,000 proteins, which can be roughly classified into four major categories: matricellular proteins, structural ECM proteins, proteoglycans and matrix-modifying proteins. Notably, matricellular proteins were the most upregulated proteins in CKD KTS, suggesting that they are important contributors to the fibrogenic niche.

Matricellular proteins

Matricellular proteins are a heterogeneous group of large, structurally unrelated ECM proteins, including tenascin C (TNC)[6,37], connective tissue growth factor (CTGF; also known as CCN2)[44], fibrillin 1 (FBN1)[42], periostin (POSTN)[45], thrombospondin 1 (TSP1)[46], secreted protein acidic and rich in cysteine (SPARC)[47] and secreted modular calcium-binding protein 2 (SMOC2)[48], that have several characteristic features[49,50] (TABLE 1). First, they are non-structural proteins but contain binding sites for ECM structural proteins, are often rapidly turned over and have regulatory roles. Second, they are generally undetectable or expressed at very low levels in normal adult tissues and organs, but are markedly induced de novo in damaged tissues after injury. Third, they harbour various common structural motifs that also exist in other matrix proteins and they can interact with a variety of cell-surface receptors, including integrins, cell-surface proteoglycans, Toll-like receptors (TLRs), growth factor receptors and scavenger receptors[51]. These properties of matricellular proteins make them the prototypical constituents of the fibrogenic niche. Matricellular proteins have critical roles in regulating a wide variety of cellular activities, including proliferation, migration, apoptosis, ECM assembly, inflammation, wound healing and fibrosis.

TNC is a major component of the kidney fibrogenic niche[6]. This hexameric glycoprotein contains an N-terminal oligomerization domain that leads to the formation of hexamers, a variable number of tandem epidermal growth factor (EGF)-like repeats, numerous fibronectin type III domains and a fibrinogen homology domain at the C terminus[52,53]. TNC is barely detectable

in adult tissues and organs but is induced after tissue injury. In several CKD models, TNC expression rapidly increases at focal sites rich in fibroblasts in the kidney parenchyma following injury[6,37]. TNC promotes fibroblast proliferation in vitro, and TNC-enriched ECM scaffold acts as a fibrogenic niche that facilitates fibroblast expansion[6]. Knockdown of *Tnc* attenuates fibroblast expansion ex vivo and reduces kidney fibrosis in vivo[6]. These findings establish TNC as a major player in organizing the fibrogenic niche that provides an optimal environment for fibroblast activation during kidney fibrogenesis.

Another well-known matricellular protein is CTGF, which is a member of the CCN family of ECM-associated heparin-binding proteins[54–56]. CTGF is expressed at low levels in normal adult kidneys and markedly upregulated in various nephropathies. It modulates cell proliferation, migration and differentiation, promotes fibrosis progression[44] and has an important role in the development of tubulointerstitial fibrosis in progressive CKD[34,55]. CTGF acts as a downstream effector of TGFβ1 and also regulates the expression and activity of TGFβ and bone morphogenetic protein (BMP)[34]. In addition, CTGF can simultaneously interact with numerous soluble factors, ligands and membrane receptors with its four domains[57].

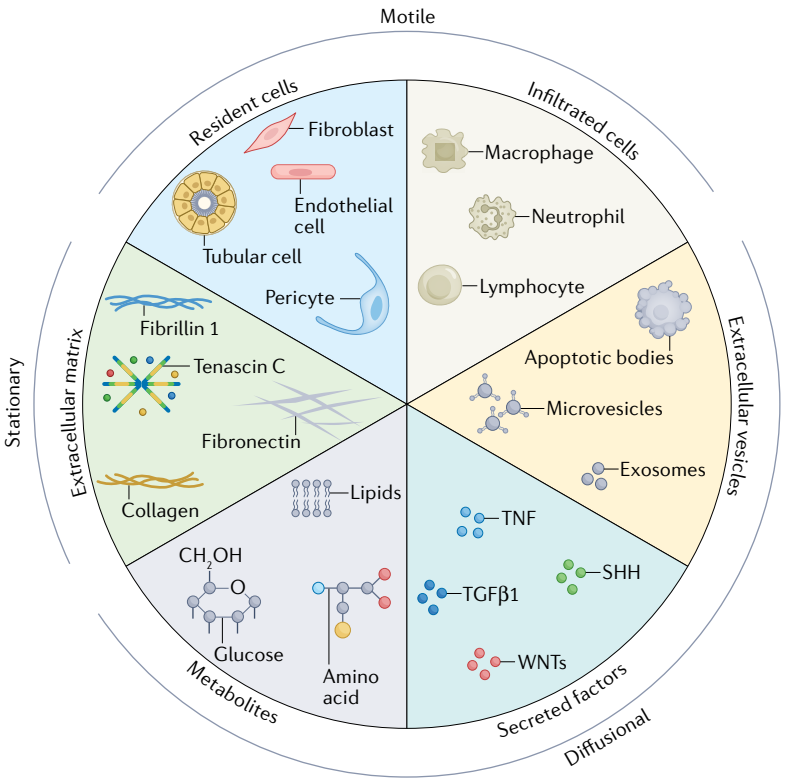

Fig. 2 | **Cellular and molecular components of the kidney fibrogenic niche.** The fibrogenic niche is formed after chronic injury and contains extracellular matrix and cellular components such as resident tubular and endothelial cells, fibroblasts and pericytes as well as infiltrated inflammatory cells. The fibrogenic niche also has high levels of extracellular vesicles, soluble factors and metabolites. The cellular components are motile in nature, whereas the extracellular vesicles, soluble factors and metabolites are diffusional. By contrast, the extracellular matrix is stationary and has a key role in organizing the formation of fibrogenic niche in a spatially defined fashion. These properties suggest that the extracellular matrix is the anchor of the fibrogenic niche in kidney fibrosis.

The diverse biological actions of CTGF depend on the cell type and tissue microenvironment.

FBN1 is a large (approximately 350 kDa), cysteine-rich ECM glycoprotein that contains multiple EGF-like motifs arranged in tandem, several domains homologous to the latent TGFβ binding protein (LTBP) and a proline-rich region[58]. It is the main component of calcium-binding microfibers and provides mechanical support for elastic and inelastic connective tissues. FBN1 is one of the most upregulated proteins in fibrotic KTS, suggesting that it is a major constituent of the fibrotic niche in diseased kidneys. FBN1 promotes apoptosis and inhibits proliferation of vascular endothelial cells in vitro[42] and knockdown of *Fbn1* prevents microvascular rarefaction and thereby impairs the progression of kidney fibrosis in vivo[42]. FBN1 is also involved in balancing skin haemostasis by forming a critical extracellular supramolecular scaffold[59].

POSTN is induced de novo at focal sites in injured kidneys during the development of CKD[50,60] and is one of the most upregulated proteins in CKD KTS[42]. Animal studies have shown that POSTN is involved in mediating kidney inflammation and fibrosis through multiple pathways, including integrin and p38 mitogen-activated protein kinase (MAPK) signalling[61,62]. Genetic or pharmacological inhibition of POSTN ameliorated the progression of CKD in animal models[61–64].

Other matricellular proteins including TSP1, SPARC and SMOC2 also have critical roles in forming the fibrogenic niche. TSP1 has been shown to regulate latent TGFβ activation, inflammation and capillary density in renal fibrosis and other fibrotic diseases[45,63,65–67]. In addition, the N-terminal domain of TSP1 can regulate collagen matrix assembly during ECM remodelling[46,66].

SPARC is a prototypical matricellular protein that regulates cell–matrix interactions and thereby influences the pathogenesis of fibrotic diseases, including renal and pulmonary fibrosis[47,68]. SPARC has a role in the regulation of cellular functions such as cell adhesion, proliferation and differentiation, and also regulates the expression and activity of numerous profibrotic growth factors.

SMOC2 belongs to the SPARC family of matricellular proteins[48,69] and is upregulated in kidney tubular epithelial cells in animal models of kidney fibrosis and in the plasma and urine of patients with CKD[48,69]. A study that used transgenic mice with overexpression or knockdown of *Smoc2* showed that this protein has a critical role in fibroblast activation and progression of kidney fibrosis[48].

Structural ECM proteins

The hallmark of tissue fibrosis is increased expression and deposition of structural ECM proteins such as collagens, fibronectin, elastin and laminins. Collagens can construct fibres, networks and filaments and are the most abundant components of the ECM[70]. The collagen superfamily consists of 28 different subtypes. Types I and III collagens are the principal components of interstitial ECM in fibrotic tissues[71]. A 2018 study showed that in mice, production of type I collagen by resident fibroblasts is essential for maintaining kidney function following unilateral ureteral obstruction (UUO), but is

Table 1 | **Major matricellular protein components of the fibrogenic niche**

Matricellular protein	Cellular sources	Targets	Main functions	Refs.
Tenascin C (TNC)	Fibroblasts	Interstitial fibroblasts, tubular epithelial cells, macrophages	Organizes the fibrogenic niche, recruits WNTs and other soluble factors, promotes fibroblast and macrophage activation and EMT	6,37
Fibrillin 1 (FBN1)	Tubular epithelial cells, podocytes	Endothelial cells, fibroblasts	Induces endothelial cell apoptosis, activates latent TGFβ via αvβ6 integrins	42
Thrombospondin-1 (TSP1)	Tubular epithelial cells	Endothelial cells, tubular epithelial cells	Participates in renal fibrosis, activates latent TGFβ, regulates angiogenesis both positively and negatively	46
Connective tissue growth factor (CTGF)	Tubular epithelial cells, mesangial cells, endothelial cells	Fibroblasts, tubular epithelial cells	Regulates the expression and activity of TGFβ, binds to various cell-surface receptors in a context-dependent manner	44
Periostin (POSTN)	Tubular epithelial cells	Tubular epithelial cells	Promotes kidney fibrosis, activates αvβ3 and αvβ5 integrins, promotes EMT	45
Secreted protein acidic and rich in cysteine (SPARC)	Mesangial cells, fibroblasts	Macrophages, fibroblasts, mesangial cells	Regulates multiple biological processes and affects extracellular matrix assembly	111
Secreted modular calcium-binding protein 2 (SMOC2)	Tubular epithelial cells	Interstitial fibroblasts	Promotes myofibroblast activation and stimulates fibroblast proliferation, migration, stress fibre formation and extracellular matrix production	48

EMT, epithelial-to-mesenchymal transition; TGFβ, transforming growth factor-β.

detrimental for kidney function in the adenine-induced nephropathy model of CKD[72].

Fibronectin is an adhesive glycoprotein with various functional motifs that can interact with glycosaminoglycans, cell-surface receptors, collagens and fibrins, thereby acting as a bridging molecule in matrix organization and assembly and in cell–matrix interactions[73]. Fibronectin extra-domain A (FnEDA) can promote myofibroblast activation and enhance the recruitment of latent transforming growth factor-β-binding protein 1 (LTBP1) to the fibroblast matrix[74].

Elastin is secreted by fibroblasts and eases the mechanical stress induced by scar tissue. This protein is expressed at very low levels in healthy mouse, rat and human kidneys, but is highly upregulated in cortical, medullar, and perivascular regions in progressive CKD[75]. In diabetic kidney disease (DKD), the deposition of laminins increases in the glomerular basement membrane and mesangial matrix, but not in the interstitium[76], suggesting that laminins might not be involved in the formation of the fibrogenic niche.

Proteoglycans

Proteoglycans consist of glycosaminoglycan chains covalently bound to a protein core. They are major constituents of the ECM that contribute to its organization and physical properties. Multiple proteoglycans are involved in the development of kidney fibrosis, including syndecans, biglycan, hyaluronan and versican. The syndecan family contains four members, which act as receptors to bind several ECM proteins, including fibronectin, collagens, growth factors and cytokines, further evoking various cell signalling pathways[77–79]. Syndecan 1 has been shown to mediate TGFβ activation during fibrosis[80]. Syndecan 4 can trap a large latent complex (which consists of a TGFβ dimer, latency-associated protein (LAP) and LTBP) and contribute to TGFβ1 activation directly or indirectly through other syndecan 4-linked pathways[81].

Biglycan is a small leucine-rich repeat proteoglycan that is expressed de novo in the interstitium in various types of CKD, including nephrotoxic serum nephritis and adriamycin nephropathy[82]. After proteolytic cleavage, biglycan can act as a soluble mediator, interact with TLRs and promote inflammatory responses[83–85].

Hyaluronan is a major component of connective tissue that is synthesized by fibroblasts. Deposition of hyaluronan has been observed in various types of CKD, including obstructive nephropathy, DKD and IgA nephropathy[86,87]. Low molecular weight hyaluron mediates inflammatory and profibrotic reactions, whereas high molecular weight hyaluron variants can exert anti-inflammatory and anti-fibrotic effects[86].

Versican is a hyaluronan-binding proteoglycan that has roles in cell proliferation, adhesion and migration as well as ECM assembly[88]. Increased versican expression in human kidney biopsy samples has been associated with progression of CKD and DKD[88].

Matrix-modifying proteins

Tissue injury is always accompanied by matrix remodelling, and ECM turnover is mediated by a large group of structurally related zinc-dependent endopeptidases known as matrix metalloproteinases (MMPs). Many MMPs, including MMP2, MMP7, MMP9 and MMP10, are upregulated in various types of CKD[89–91]. Collectively, these MMPs can degrade all types of ECM proteins. MMPs can also cleave many non-ECM substrates, such as E-cadherin, tight junction protein ZO1, FAS ligand, nephrin and heparin-binding EGF-like growth factor (HBEGF)[92–96]. They have critical roles not only in ECM remodelling but also in cell adhesion, proliferation, apoptosis and inflammation.

Crosslinking of ECM proteins

The ECM network in the fibrogenic environment is modified by crosslinking, which renders it resistant to degradation. Proteomics analyses have shown that tissue transglutaminase 2 (TG2; also known as TGM2) and lysyl oxidase homologue 2 (LOXL2) are enriched in fibrotic KTS[42]. TG2 is a multifunctional enzyme that catalyses the crosslinking of ECM proteins[97], whereas Loxl2 is an extracellular copper-dependent amine oxidase that mediates the formation of crosslinks in collagens and elastin[98]. The ECM proteins in the fibrogenic niche could potentially be unique in that they are substantially modified as a function of fibrogenesis.

Role of the fibrogenic niche in fibrogenesis

The ECM proteins discussed above constitute the backbone of the fibrogenic niche in kidney fibrosis[11]. Together with secreted extracellular vesicles and pro-fibrotic factors, these proteins build a local microenvironment that not only promotes fibroblast activation and proliferation but is also instrumental in mediating infiltration of inflammatory cells, microvascular rarefaction and tubular atrophy (FIGS. 1,2). Exactly what triggers the formation of the fibrogenic niche after kidney injury is an unresolved question. One can speculate that the initial tubular injury causes the release of soluble factors, such as SHH, WNTs and TGFβ, that induce interstitial fibroblasts to express TNC, which is the primary organizer of niche formation[6,99]. Furthermore, it is possible that diverse cell types contribute the ECM components in the fibrogenic niche at different stages of CKD. For example, TNC is de novo induced in interstitial fibroblasts in the early stage after injury and is expressed in tubular epithelium in the advanced stage of CKD[6,37,100]. Such dynamic changes of the ECM components and their sources could influence the evolution of kidney injury repair and fibrogenesis. Whether distinct disease aetiologies such as DKD and IgA nephrology have different effects on the formation and composition of the fibrogenic niche remains to be investigated.

As decellularized KTS preserve the composition and integrity of the kidney ECM, they provide an unprecedented ex vivo model system to investigate the effect of the fibrogenic niche on kidney cells in the 3D context. When seeded onto KTS of fibrotic kidneys from animal models of CKD, fibroblasts proliferate, tubular cells undergo EMT, macrophages are activated and endothelial cells undergo apoptosis[6,37,42]. These findings demonstrate that KTS from fibrotic kidneys reproduce the fibrogenic microenvironment in vivo.

Fibroblast activation

Fibroblast activation, characterized by αSMA expression and production of a large amount of ECM components, is the most important event in kidney fibrogenesis[101]. The majority of studies have largely focused on the roles of soluble factors such as TGFβ1, FGF2, PDGF, SHH and WNTs in triggering fibroblast activation[14,16,102,103]. However, we found that normal kidney fibroblasts (NRK-49F) that are inoculated on TNC-enriched decellularized ECM scaffolds spontaneously proliferate in the absence of profibrotic factors, suggesting a predominant role of the extracellular microenvironment in fibroblast activation[6]. Furthermore, exogenous recombinant TNC promotes fibroblast proliferation in vitro and induces the expression of multiple proliferation-related genes[6]. KTS prepared from CKD kidneys also promote fibroblast proliferation ex vivo and this effect can be abolished by depleting TNC from the KTS[6].

Several other profibrotic ECM components can also promote fibroblast activation. For example, FnEDA can promote fibroblast activation in various fibrotic conditions[104], and mice that are deficient in FnEDA are protected against organ fibrosis[105]. Hyaluronan also promotes and sustains fibroblast activation in a TGFβ1-dependent manner and stabilizes cell–ECM adhesion[87].

Tubular injury

Tubular epithelial cells in the fibrotic microenvironment are subjected to changes such as partial EMT, cell-cycle arrest, senescence and apoptosis, leading to tubular atrophy[13]. When primary tubular epithelial cells or a tubular cell line (HKC-8) are cultivated in TNC-rich KTS, they undergo partial EMT, as evidenced by loss of E-cadherin and induction of vimentin, αSMA and fibroblast-specific protein 1 (FSP1; also known as S100A4)[37]. Furthermore, TNC induces tubular cells to undergo partial EMT in vitro[37], suggesting a central role of the tissue microenvironment in regulating tubular cell integrity. We speculate that the fibrogenic niche might also induce tubular cell-cycle arrest and senescence, but this hypothesis remains to be tested.

Collagens in the ECM also have a role in regulating the phenotype and integrity of tubular epithelial cells. Type IV collagen IV has been reported to maintain the epithelial cell phenotype of proximal tubular cells, whereas type I collagen promotes EMT[106].

CTGF can enhance the expression of integrin-linked protein kinase (ILK) in tubular epithelial cells and promote EMT in a dose- and time-dependent manner[107]. TSP1 induces rat proximal tubular cell apoptosis via caspase 3 activation, and knockout of *Tsp1* in mice preserves tubular integrity after renal ischaemia–reperfusion injury or UUO[67]. POSTN has been shown to impair the renal tubular epithelial phenotype and promote EMT during the pathogenesis of CKD[45,50].

Inflammation

Inflammation is a key component of kidney fibrosis, and the fibrogenic niche facilitates infiltration of inflammatory cells. When macrophages are seeded on decellularized KTS from fibrotic kidney, they proliferate and secrete pro-inflammatory cytokines (J. Liao and Y. L., unpublished observations). TNC is reported to act as a damage-associated molecular pattern (DAMP) and sustain inflammation through TLR4-mediated NF-κB signalling[108]. Several other ECM proteins have been shown to promote inflammatory cell infiltration during kidney fibrosis. For example, CTGF induces macrophage accumulation by upregulating the renal expression of chemokines and cytokines[109]. POSTN is reported to orchestrate inflammatory and fibrotic responses via β3 integrin–focal adhesion kinase (FAK) signalling

in CKD[62]. TSP1 has a pro-inflammatory effect on macrophages by stimulating TLR4 expression[110]. SPARC can recruit neutrophils to sites of acute inflammation and stimulate polarization of peritoneal macrophages to a pro-inflammatory M1 phenotype and *Sparc*-knockout mice showed reduced renal inflammation and fibrosis after kidney injury compared with wild type controls[111,112].

Proteoglycans such as biglycan can act as DAMPs and trigger inflammation by interacting with innate immune receptors[84,113,114]. Biglycan promotes recruitment of pro-inflammatory M1 macrophages and neutrophils into the kidney by triggering NF-κB, p38MAPK and extracellular signal-regulated kinase (ERK) signalling[84]. A process of macrophage-to-myofibroblast transition has been reported to occur during kidney fibrogenesis[115,116] and could potentially have a role in the formation of the fibrogenic niche. Conversely, the fibrogenic niche might be instrumental in facilitating macrophage-to-myofibroblast transition.

Vascular rarefaction

Vascular rarefaction due to endothelial cell dysfunction or dropout is a hallmark of advanced kidney fibrosis. Early studies of vascular rarefaction in CKD largely focused on the dysregulation of soluble angiogenesis factors such as vascular endothelial growth factor (VEGF)[117]. However, in 2021, we showed that changes in the ECM microenvironment have an important role in vascular rarefaction in CKD[42]. When human endothelial cells were inoculated onto KTS prepared from fibrotic kidneys, they expressed a host of proapoptotic proteins and underwent apoptosis. Our analyses identified FBN1 in the fibrogenic microenvironment as a key protein that induces endothelial cell apoptosis and inhibits their proliferation in response to mitogen in vitro. These findings clearly indicate that the FBN1-enriched fibrogenic niche is a hostile environment for endothelial cells that promotes microvascular rarefaction.

TSP1 is a potent endogenous inhibitor of angiogenesis that directly inhibits endothelial cell migration, proliferation and survival and antagonizes the activity of VEGF[46]. TSP1 can antagonize the binding of FGF2 and VEGF to their receptors to prevent angiogenesis, while promoting the binding of PDGF to mesenchymal stromal cells to induce their proliferation and migration[118]. In a UUO model, inhibition of TSP1 using a short hairpin RNA (shRNA) increased VEGF expression and peritubular capillary density[119].

Endothelial-to-mesenchymal transition has also been proposed to contribute to vascular rarefaction and kidney fibrosis[120,121]. Further studies are needed to investigate whether the fibrogenic niche surrounding the capillary has a role in endothelial-to-mesenchymal transition.

Cell–cell communication

Kidney fibrogenesis involves most, if not all, kidney-resident cells and infiltrating cells at various points in the process. Thus, cell–cell communication and crosstalk have indispensable roles in coordinating responses in the fibrotic kidney. In addition to communication between adjacent cells using gap junctions, tight junctions and desmosomes, cell–cell communication between cells without direct contacts is assumed to be mediated by secreted soluble factors in a paracrine fashion. For example, tubular epithelial cells can control fibroblast activation by secreting profibrotic factors such as SHH, WNTs and TGFβ1 (REFS.[103,122–124]). Extracellular vesicles might also mediate cell–cell communication after kidney injury[125]. Communication facilitated by extracellular vesicles is efficient and robust because their contents include various RNAs, lipids and metabolites as well as soluble factors.

The formation of the fibrogenic niche suggests a completely new mode of cell–cell communication in a spatially confined area. It is conceivable that ECM components secreted by one type of cells contribute to the formation of the fibrogenic niche, which in turn affects the behaviour of other cells in the close vicinity. For example, TNC is secreted by activated fibroblasts and orchestrates a fibrogenic niche that not only promotes fibroblast activation but also triggers tubular EMT[6,37]. Similarly, damaged renal tubular epithelial cells upregulate FBN1, which creates a hostile environment that induces endothelial cell apoptosis[42]. Intercellular communication mediated by ECM proteins is unique in that it operates focally in a spatially confined setting.

Mechanisms of action of the fibrogenic niche

How the fibrogenic niche affects the behaviour of neighbouring cells and thereby changes the course of disease remains to be fully elucidated. ECM proteins can anchor cells to certain spatial locations via integrin binding and the fibrotic ECM typically has greater tissue stiffness than normal ECM[126], as the collagen fibres align and bundle in fibrotic kidney tissue that experiences shear force. The mechanical stress exerted by the stiffness of fibrotic ECM facilitates fibroblast activation[127]. In addition, ECM proteins in the fibrotic niche can recruit and present soluble factors, activate signalling pathways that control cell behaviour and be digested by MMPs, resulting in the generation of bioactive matrikines[128] (FIG. 3).

Recruitment and presentation of soluble factors

The fibrogenic niche seems to recruit and concentrate soluble factors from the surrounding extracellular space, thereby creating a signal reservoir and a microenvironment with high levels of profibrotic factors. TNC might have a role in this process as it promiscuously binds a variety of profibrotic factors, including TGFβ1, PDGF and FGF2, with high affinity[129]. We found that TNC-rich KTS from fibrotic kidney could recruit WNT ligands from the surrounding media[100]. As TNC is a large hexameric protein that can potentially bind to multiple WNTs at the same time, this mechanism could create a unique microenvironment in which the local concentration of WNTs is highly enriched. The injured tubular epithelium is the major source of WNTs in CKD[124] and TNC-mediated recruitment might explain how tubule-derived WNTs home in the fibrogenic niche. TNC might act as a molecular sponge that attracts and recruits profibrotic factors including WNTs and TGFβ1 from the surrounding extracellular milieu.

ECM proteins that recruit and bind soluble factors might also have a critical role in presenting various ligands to their cognate cell-surface receptors. In contrast to soluble factors that are free in solution, ECM-bound factors would likely be presented to their cell-surface receptors focally and with high abundance, leading to receptor activation and subsequent signalling.

Activation of signalling pathways

ECM proteins in the fibrogenic niche may exert their biologic activities by engaging with membrane receptors and activating diverse signalling pathways. Several well-characterized cellular receptors such as integrins, TLRs and low-density lipoprotein receptor-related protein 6 (LRP6) are known to transmit signals triggered by ECM proteins enriched in the fibrogenic niche. Cells that reside in the fibrogenic niche could be activated by ECM components via these receptor-mediated signals.

Integrins. Integrins are a large family of typical ECM receptors that are composed of α and β heterodimers formed by 18α and 8β subunits. At least 24 different α/β integrin heterodimers have been reported; these heterodimers bind to a variety of ECM proteins with different affinities[130,131]. Integrins are bridging molecules that connect the ECM and cell cytoskeleton[51,132] and provide a signalling hub between ECM and cells[133]. Activation of integrins by ECM proteins triggers subsequent focal adhesion kinase (FAK) and ILK, leading to activation of MAPK and β-catenin, respectively[132].

As a receptor for fibronectin, αv integrin is a key modulator in kidney fibrosis[134]. αv Integrin expressed by fibroblasts binds to latent TGFβ and stimulates its activation. Knockout of *Itgav* in myofibroblasts attenuated fibrosis in mouse kidney[135]. The epithelial-specific αvβ6 integrin is a receptor for many ligands of ECM proteins, including TNC, FBN1, fibronectin and the LAP of TGFβ[37,42,136]. TNC impairs tubular integrity via activation of the αvβ6 integrin–FAK–ERK signal cascade[37]. FBN1 activates αvβ6 integrin–TGFβ signalling to induce endothelial cell apoptosis[42]. By binding to αvβ3, α3β1, α4β1 and α5β1 integrins, TSP1 regulates cell adhesion and migration[46]. CTGF induces α5β1 integrins and mediates TGFβ-induced fibronectin deposition[137].

TLR4. TLRs have important functions in innate and adaptive immunity. TLR4 is constitutionally expressed in proximal tubular epithelial cells and has a role in the pathophysiology of various kidney diseases[138]. Loss-of-function mutation or knockout of *Tlr4* can alleviate inflammatory damage and renal fibrosis in various models of CKD[139–141]. Upon ligand binding, TLR4 recruits myeloid differentiation primary response protein MyD88 and subsequently activates NF-κB and MAPK and promotes the release of pro-inflammatory cytokines.

Numerous ECM proteins can act as TLR4 ligands and thereby elicit immune responses. For example, binding of TNC to TLR4 induces collagen synthesis and secretion of IL-6 and TGFβ. TNC also regulates M1/M2 macrophage polarization through binding to TLR4 (REF.[142]). Moreover, in damaged tissues, TLR4 signalling induces TNC, thereby forming a vicious cycle[143]. FnEDA in the fibrotic microenvironment drives continuous fibroblast activation through TLR4 (REF.[144]). In addition, biglycan acts as an endogenous ligand of TLR4 in macrophages and mediates innate immunity, leading to rapid activation of NF-κB, p38 MAPK and ERK and induction of tumour necrosis factor (TNF)[145].

LRP6. LRP6 is a single-pass transmembrane protein. As a co-receptor for WNT ligands, LRP6 acts in concert with Frizzled receptors and is essential for WNT signal

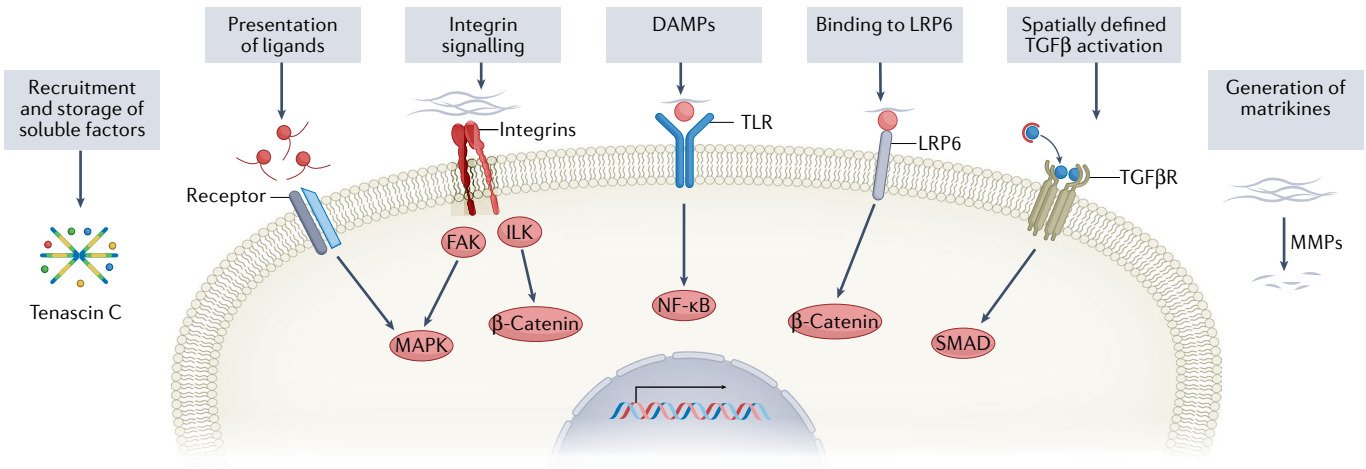

Fig. 3 | **Modes of action of matricellular proteins.** Matricellular proteins can act as signal reservoirs by recruiting and enriching growth factors and cytokines from the extracellular milieu. They can function as signal presenters to facilitate binding of extracellular matrix (ECM)-associated ligands to their plasma membrane receptors. They can also control cell behaviour through classical integrin–focal adhesion kinase (FAK)–mitogen-activated protein kinase (MAPK) signalling or integrin-linked protein kinase (ILK)–β-catenin signalling. In addition, matricellular proteins can function as damage-associated molecular patterns (DAMPs), bind to Toll-like receptors (TLRs) and activate nuclear factor-κB (NF-κB) signalling. They can also bind to low-density lipoprotein receptor-related protein 6 (LRP6) and trigger β-catenin signalling via a mechanism that is independent of WNT signalling. Matricellular proteins can also control the post-translational, spatially defined activation of transforming growth factor-β (TGFβ) by interacting with αvβ6 integrins. They can also be digested by matrix metalloproteinases (MMPs) to generate bioactive matrikines. TGFβR, TGFβ receptor.

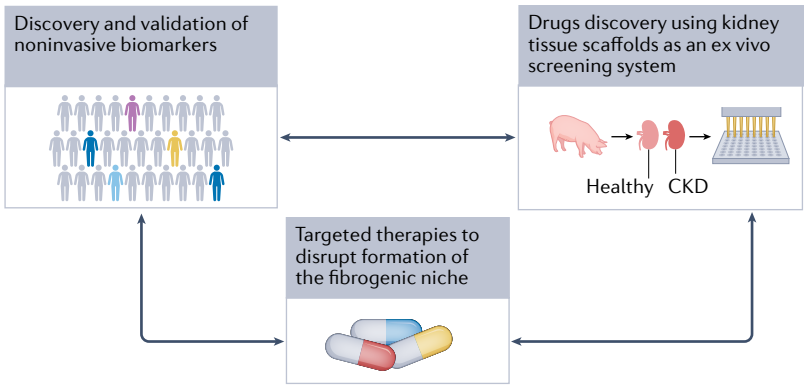

Fig. 4 | **Potential clinical implications of the kidney fibrogenic niche hypothesis.** The concept of the fibrogenic niche could have the potential to revolutionize the future diagnosis, prevention and treatment of fibrotic chronic kidney disease (CKD). Serum or urinary levels of individual extracellular matrix proteins as well as their modifying enzymes (such as matrix metalloproteinases) could be developed as non-invasive biomarkers for the detection and monitoring of kidney fibrosis. Decellularized kidney tissue scaffolds from animal models could be harnessed as unique ex vivo screening platforms for anti-fibrotic drug discovery. Furthermore, targeted approaches that disrupt the formation of the fibrogenic niche could be developed as therapies for the prevention and treatment of fibrotic CKD.

transduction[146]. WNT–β-catenin signalling is involved in the onset and development of renal fibrosis[147–149]. Functional blocking of LRP6 inhibited WNT signalling and mitigated renal fibrosis in a type 1 diabetes model[150]. LRP6 is expressed by pericytes and acts as a co-receptor for multiple growth factors such as PDGF and TGFβ, which have roles in pericyte activation and transition to myofibroblasts[151].

Multiple ECM proteins of the fibrogenic niche can bind to LRP6 and activate its downstream signalling. For example, biglycan has been shown to affect β-catenin-mediated transcription by interacting with the LRP6 receptor[152,153]. Moreover, fibronectin type III domain containing protein 4 (FNDC4) activates WNT–β-catenin signalling via LRP6 phosphorylation[154]. The R-spondin family proteins can also promote LRP6 phosphorylation and directly activate WNT–β-catenin signalling[155]. In addition, CTGF can activate LRP6 and stimulate the ERK and JUN N-terminal kinase (JNK) pathways[151,156].

Activation of TGFβ1

The components of the fibrogenic niche have a role in mediating the site-specific activation of TGFβ1, which is a central driver of renal fibrosis[35]. We showed that FBN1 controls the bioavailability and activation of TGFβ1 stored in the extracellular space by interacting with αvβ6 integrins, without affecting total TGFβ1 expression[42]. As FBN1 is a stationary ECM protein, it dictates TGFβ1–SMAD3 activation in a spatially confined manner in situ. This spatially defined activation could be crucial to reach the signal threshold in a specific locality and cause vascular rarefaction in CKD.

TSP1 is a primary activator of latent TGFβ1. Binding of TSP1 to LAP forms an active ternary LAP–TSP1–TGFβ1 complex that mediates TGFβ1 activation[46]. CTGF can activate TGFβ1, increase SMAD2 and/or SMAD3 phosphorylation and promote the transcription of SMAD-responsive genes including *CCN2*, which encodes CTGF[55]. ECM stiffness also facilitates the release of active TGFβ1 in situ and myofibroblast activation through various mechanotransduction pathways and molecular mediators such as transcriptional coactivator YAP1, transforming protein RHOA–RHO-associated protein kinase 1 (ROCK1) and integrins[157–160]. By engaging with integrins, TLR4 and LRP6, as well as activating TGFβ, ECM proteins in the fibrogenic niche could eventually trigger the activation of β-catenin, NF-κB and SMAD3, the triad of core transcriptional regulators that drive the expression of profibrotic and pro-inflammatory genes.

Generation of matrikines

Notably, ECM components, particularly matricellular proteins, constantly undergo remodelling after tissue injury. This remodelling could lead to the generation of matrikines that have important roles in regulating cellular activities[161]. As few data are available on matrikines generated from ECM proteins in the fibrogenic niche, further studies are warranted to investigate their potential role in kidney fibrosis.

Clinical implications

The concept of the fibrogenic niche transforms the existing view of the initiation and development of kidney fibrosis, which emphasizes the importance of specific signalling pathways, such as the TGFβ and WNT–β-catenin pathways, and cell types, such as fibroblasts, pericytes, tubular cells and macrophages. By contrast, the fibrogenic niche hypothesis focuses on the formation and evolution of the profibrotic microenvironment after tissue injury. Knowledge of the fibrogenic niche could eventually translate into the identification of novel biomarkers, the discovery of new drugs and the development of targeted therapies for fibrotic CKD (FIG. 4).

Non-invasive biomarkers

Currently, diagnosis of renal fibrosis relies on kidney biopsy, an invasive procedure with substantial associated risk. As renal fibrotic lesions are not uniform, core needle biopsy is inherently associated with sample errors[162,163]. Therefore, a pressing need exists to identify non-invasive serum or urine biomarkers for early detection and prognostic assessment of kidney fibrosis.

An increasing number of studies have shown that ECM components can be harnessed as novel non-invasive biomarkers[164] (TABLE 2). Urinary TNC has been identified as a sensitive biomarker of early kidney fibrosis[37]. Levels of urinary TNC in patients with CKD are closely associated with the severity of kidney dysfunction and are increased in those with early CKD who have relatively normal kidney function (estimated glomerular filtration rate >90 ml/min/1.73 m^2)[37]. Serum FBN1 level also correlates with kidney insufficiency in patients with CKD and can be used as a biomarker of vascular damage[42]. Urinary POSTN has been suggested as an early biomarker of renal injury in CKD and the ratio of urinary POSTN to creatinine was reported to predict the renal outcomes of patients with IgA nephropathy[165,166]. Furthermore, the levels of urinary

Matrikines
Peptides that are liberated by partial proteolysis of extracellular matrix proteins such as collagens, fibronectin, laminins, elastin and matricellular proteins. Matrikines are able to regulate biological processes and often have activities that are different from those of their parent proteins.

Table 2 | **Extracellular matrix and related proteins as non-invasive biomarkers of kidney fibrosis**

Protein	Source	Comments	Ref.
Tenascin C (TNC)	Urine	Indicates fibroblast activation in the early stages of fibrogenesis; urinary levels are substantially elevated in patients with stage 1 CKD (eGFR >90 ml/min/1.73 m^2)	37
Fibrillin 1 (FBN1)	Serum	Marker of vascular rarefaction in CKD; serum levels correlate inversely with eGFR and positively with serum creatinine, blood urea nitrogen and cystatin C	42
Periostin (POSTN)	Urine	Urinary POSTN to creatinine ratio at initial diagnosis correlates with renal fibrosis and predicts the prognosis of patients with IgAN	165
Matrix metalloproteinase 7 (MMP7)	Urine	Urinary levels correlate with renal fibrosis in patients with CKD; MMP7 predicts the progression of IgAN; MMP7 outperforms angiotensinogen, epidermal growth factor, KIM1 and serum galactose-deficient IgA1 for the prediction of IgAN progression	167
Matrix metalloproteinase 10 (MMP10)	Serum	Predicts the progression of proteinuric CKD; serum pro-MMP10 levels correlate inversely with eGFR and positively with serum creatinine, cystatin C and proteinuria	92

CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; IgAN, IgA nephropathy.

MMP7 and serum MMP10 are potential non-invasive biomarkers of kidney fibrosis in patients with CKD[37,167].

The detection of ECM protein and modifying enzyme biomarkers might reflect different aspects and stages of renal fibrogenesis. For example, uTNC could be a marker of fibroblast activation in the injured kidney, indicating active fibrogenesis in the early stage of CKD[6]. By contrast, serum FBN1 might be a marker of microvascular rarefaction in the late stage of nephropathies[42]. Furthermore, ECM biomarkers differ in whether they are present in urine or serum. For instance, TNC and MMP7 are present at high levels in the urine of patients with CKD[37,167], whereas FBN1 and MMP10 are mainly present in the serum of these patients[42,92]. A panel of biomarkers might be more accurate than a single biomarker for predicting and monitoring renal fibrosis, but more studies are needed to test this hypothesis.

Drug screening

Currently, no treatment regime is specifically targeted at renal fibrosis. This tremendous unmet medical need necessitates rethinking the existing screening and discovery approaches for anti-fibrotic drugs. The current strategy for developing these drugs relies on in vitro screening platforms, which are typically designed to test whether a drug inhibits a particular profibrotic signalling pathway[5,168]. As kidney fibrogenesis involves multiple cell types and signalling pathways, a precise and more sophisticated screening system that closely imitates the renal fibrogenic microenvironment is required.

As decellularized KTS from fibrotic kidney faithfully models the fibrogenic microenvironment in vivo, it can be utilized as a unique ex vivo screening platform for the identification of anti-fibrotic drugs. When seeded on fibrotic KTS, fibroblasts are autonomously activated, proliferate and produce a large amount of ECM in the 3D context. Using large animal models such as pigs, a considerable amount of KTS can be obtained from fibrotic kidneys to carry out large-scale ex vivo screening. We used decellularized KTS prepared from fibrotic pigs as a platform to screen a small molecule chemical library and discovered a small molecule compound that disrupted the formation of the fibrogenic niche (Xue Hong and Y. L., unpublished observations). These results provide proof-of-principle that decellularized KTS can be used as a unique ex vivo screening platform for anti-fibrotic drugs, potentially providing an alternative to traditional in vitro cell culture screening and time-consuming and expensive animal experiments. More studies are needed to validate these findings.

Targeted therapy

The concept of the fibrogenic niche might have important implications for the future treatment of kidney fibrosis. Current treatments for CKD slow or delay disease progression but do not halt or reverse renal fibrosis. Strategies that are in development to target renal fibrosis mostly focus on enzymes closely related to ECM haemostasis, including ECM biosynthetic enzymes and molecular chaperones, proteases that process and degrade ECM, and enzymes involved in collagen crosslinking and assembly[169,170]. As these enzymes are usually multifunctional[90,92,171], such treatments could potentially trigger immunological responses or other adverse effects.

As the formation of the fibrogenic niche is a crucial step in the initiation of kidney fibrosis, targeting and disrupting its assembly could be an effective therapeutic strategy. Unlike strategies that target a single pathogenic process or signalling pathway with a role in renal fibrogenesis, therapies that target the fibrogenic niche could potentially prevent the initial step in fibrogenesis. To identify such therapies, new small molecule compounds could be screened, discovered and developed using a decellularized KTS ex vivo screening system. Novel matrikines or peptides that interfere with fibrogenic niche formation could also be designed, characterized and produced[172]. Engineered extracellular vesicles or nanoparticles with specific integrin profiles could also be developed as a vehicle for delivering therapeutic drugs to the fibrogenic niche. Currently, no novel therapeutics that target formation of the fibrogenic niche are in development. However, these potential strategies and efforts to discover new agents that dismantle the fibrogenic niche could ultimately lead to the development of more effective anti-fibrotic therapies.

Conclusions and future perspective

The fibrogenic niche is a unique microenvironment in a spatially confined setting. Structural elements of the fibrogenic niche include cellular components, extracellular vesicles and secreted factors, as well as a specialized ECM network. Unlike other elements of the fibrogenic niche that are either motile or diffusional, ECM proteins are stationary and act as the anchor of the fibrogenic niche. Decellularized ECM scaffolds from fibrotic kidneys preserve the fibrogenic environment and autonomously promote fibroblast proliferation, tubular EMT, macrophage activation and endothelial cell apoptosis ex vivo, thereby recapitulating key events in the pathogenesis of CKD. These findings highlight a central role of the tissue microenvironment in the initiation and development of kidney fibrosis. The microenvironment-centric concept of the fibrogenic niche represents a paradigm shift in understanding of the mechanism of fibrosis that might have profound implications for the detection, drug development and therapeutic intervention of not only CKD but also fibrotic diseases of other organs.

However, many knowledge gaps require further investigation. For example, knowledge of how kidney-resident cells within the fibrotic environment behave and interact with their surroundings is scant and inadequate. The transcriptome and proteome of kidney cells needs to be decoded with spatial dimension and their spatial biology needs to be studied at the single-cell level within the 3D context[173–175]. Another open question is how the ECM network in the fibrogenic niche recruits and builds a special microenvironment enriched with extracellular vesicles and secreted soluble factors. To what extent different aetiologies of CKD affect the composition and dynamics of the fibrogenic niche formation is also unclear. Finally, the identification of strategies to disrupt the formation of the fibrogenic niche and enable the development of effective therapies to prevent or reverse fibrosis remains challenging. A comprehensive understanding of these areas could ultimately translate into novel therapies for millions of patients with CKD.

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Y.L. conceived the article and provided the outlines of the manuscript. L.L. researched data for the article. L.L. and Y.L. wrote the manuscript. L.L. and H.F. made the figures. All authors made substantial contributions to discussions of the content and edited the manuscript before submission.

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